REMARKS

Reconsideration of this application is respectfully requested.

Claims 183-318 and 325-717 were previously pending in this application. Those claims have been canceled in favor of newly-added claims 718-1110. Accordingly, claims 718-1110 are presented for further examination on the merits.

Applicants and their attorney acknowledge with appreciation the indication from the Examiner that the final Office Action mailed on December 8, 1998 has been withdrawn due to processing and delivery circumstances. It is understood and appreciated that the response time has been restarted as of the September 7, 2000 mailing date of the instant Office Action.

Acknowledgement is also made that the art unit designated for this application has been changed. Henceforth, any and all future correspondence will be directed to Group Art Unit 1631.

Applicants also appreciate the indication in the September 7, 2000 Office Action that the rejections and/or objections not reiterated from previous office actions have been withdrawn and that other rejections and/or objections are either reiterated or newly applied.

Finally, Applicants wish to thank Examiner Marschel for his time and courtesy extended to Dr. Engelhardt and their attorney at the December 5, 2000 interview.

A new title of the invention has been submitted. This new title, "Arrays for Nucleic Acid Applications, And Other Compositions and Systems Comprising Chemically Labeled Oligonucleotide or Polynucleotide," is believed to be more descriptive of Applicants' claimed invention herein.

A new abstract has also been submitted. Attached to this Amendment as Exhibit 1, the new abstract is believed to be more descriptive of the present invention and in conformance with the Manual of Patent Examining Procedure.

(MPEP) §608.01(b) [Guidelines For The Preparation Of Patent Abstracts, pages 600-51 and 600-52]. As such, the new abstract should enable future readers to ascertain quickly the character of Applicants' subject matter covered by their disclosure, including that which is new in the art to which the present invention pertains.

The first page of the specification has been amended to include a section cross-referencing the instant application with other related applications and patent in the family. This amendment follows in response to the Examiner's remarks in the September 7, 2001 Office Action (page 2, last paragraph, through page 3, first paragraph). A previous claim for priority under 35 U.S.C. §120 had been made in Applicants' October 28, 1992 Preliminary Amendment Accompanying Request For Continuation Application Under 37 C.F.R. §1.60 submitted in connection with previous U.S. Patent Application Serial No. 07/967,646. The present application was then filed as a file wrapper continuation under 35 U.S.C. §1.62 on June 7, 1995, thus preserving the earlier amendments to the specification, including Applicants' previous claim for priority under 35 U.S.C. §120. Accordingly, in order to comply fully with the Examiner's suggestions as set forth in the Office Action, a new section for such priority claim has been inserted above.

The specification has also been amended to recite subject matter that was disclosed in the originally filed claims. The originally filed claims were numbers 23-26 from U.S. Patent Application Serial No. 06/732,374, filed on May 9, 1985.

Entry of the above amendments to the specification and the new title and abstract is respectfully requested.

As indicated above, new claims 718-1110 have been added in place of the former and now canceled claims 183-318 and 325-717. The new claims are drawn to a solid support (claims 718-872), a composition of matter (873-1026) and a transparent non-porous or translucent non-porous system (1027-1110).

In further detail, claims 718-872 are directed to a solid support comprising an array of substrate surfaces, each substrate surface comprising a fixed or immobilized nucleic acid strand. In the case of claims 718-799 and as recited in the main claim (718), at least one double-stranded nucleic acid is fixed or

immobilized to the substrate surface and at least one strand comprises one or more non-radioactive chemical label or labels which comprise a non-radioactive signaling moiety or moieties which are quantifiable or detectable. Further, at least one nucleic acid strand or a sequence therefrom in one of the substrate surfaces is different from at least one other nucleic acid strand or a sequence therefrom in another substrate surface. Dependent embodiments are given in claims 719-799, including a collection or set of such solid supports (claims 793-797) and a system for retaining or containing a fluid or solution, which system comprises such solid support (claims 798-799).

Claims 800-872 are directed to another aspect or feature of Applicants' claimed nucleic acid array subject matter. As set forth in claim 800, which is independent, a non-porous solid support is provided which comprises an array of substrate surfaces. Each such surface comprises at least one fixed or immobilized nucleic acid strand and at least one nucleic acid strand or a sequence therefrom in one of the substrate surfaces is different from at least one other nucleic acid strand or a sequence therefrom in another substrate surface. Dependent embodiments are given in claims 801-872, including a collection or set of such solid supports (claims 869-871) and a non-porous system for retaining or containing a fluid or solution, which system comprises such solid support (claim 871) or a collection or set of any such solid supports (claim 872).

Claims 873-1026 are directed to compositions of matter. In claims 873-955, a composition of matter is claimed which comprises a transparent non-porous or translucent non-porous system containing a fluid or solution. As set forth in claim 873, which is independent, the system comprises four elements. The first element is (i) a solid support contained within the transparent non-porous or translucent non-porous system and the second element is (ii) a double-stranded oligonucleotide or polynucleotide which is directly or indirectly fixed or immobilized to the solid support. Recited as the third element is (iii) a chemical label or labels attached to one of the strands, the label or labels comprising a signaling entity or entities which are quantifiable in or from the fluid or solution or in or through the system, the quantity being proportional to the amount or quantity of the label or labels. The fourth element in claim 873 is (iv) photometric means for quantifying said quantifiable signaling entity or entities. Various dependent embodiments of the subject matter of claim 873 are given in claims 874-955.

Claims 956-1026 are directed to a different composition of matter. As set forth in claim 956, which is independent, a composition of matter is provided which comprises a transparent non-porous or translucent non-porous system containing a fluid or solution. The system is defined as comprising a double-stranded oligonucleotide or polynucleotide which is directly or indirectly fixed or immobilized to the transparent non-porous or translucent non-porous system. A chemical label or labels is attached to one of the strands. The label or labels comprise a signaling entity or entities which are quantifiable in or from the fluid or solution or in or through the system. The quantity of signal is proportional to the amount or quantity of the label or labels. Also provided as an element of claims 956-1026 are photometric means for quantifying said quantifiable signaling entity or entities. Claims 957-1026 provide further embodiments of the invention defined in claim 956.

Lastly, claims 1027-1110 are directed to a transparent non-porous or translucent non-porous system containing a fluid or solution. The system comprises four elements, including a double-stranded nucleic acid, chemical label or labels, a solid support and photometric means for quantification. In further detail, the first element in claim 1027, which is independent, is (i) a double-stranded nucleic acid comprising an oligonucleotide or polynucleotide hybridized or hybridizable to an oligo- or polynucleotide sequence. The second element is (ii) a chemical label or labels attached to one of the strands, the chemical label or labels comprising a signaling entity or entities which are quantifiable in or from the fluid or solution or in or through the system, the quantity being proportional to the amount or quantity of the label or labels. The third element recited in claim 1027 is (iii)a solid support contained within the transparent non-porous or translucent non-porous system, the solid support having directly or indirectly fixed or immobilized thereto the oligo- or polynucleotide sequence or the oligonucleotide or polynucleotide (i). As in the case of the other compositions and systems now claimed, the fourth element in claim 1027 are (iv) photometric means for quantifying said quantifiable signaling entity or entities.

It is believed that new claims 718-1110 will serve to ultimately address many of the new matter and indefiniteness issues raised in the September 7, 2000 Office Action. It is also believed that no new matter issues will be raised by the

presentation and entry of the new claims.

The Rejection Under 35 U.S.C. 112, First Paragraph

Claims 189-192, 196, 205-207, 233-236, 245-247, 275, 277-280, 293-295, 325-376, 379, 381, 382, 387, 389, 390, 395, 397, 398, 405, 407-410, 414, 423-425, 451-454, 463-465, 493, 495-498, 502, 511-513, 539, 541, 542, 547, 549, 550, 555, 557, 558, 565, 567-570, 574, 582-584, 610-613, 621-623, 651, 653-656, 660, 668-670, 696, 698, 699, 704, 706, 707, 712, 714, and 715 stand rejected for new matter under 35 U.S.C. §112, first paragraph. In the Office Action (pages 4-5), the Examiner stated:

> A thorough review of the instant application has revealed that several of the claims now contain NEW MATTER which was not disclosed as filed. The following NEW MATTER limitations are listed with the respective claims in which they are contained directly or due to dependence from a claim which contains the NEW MATTER. It is noted that basis was pointed to for many of these limitations in the amendment, filed 5/19/99. These are commented on below as appropriate. It is additionally noted that this 5/19/99 amendment cited previous claims as support for several presently pending claims, but that none of these previous claims were original claims but rather claims which were filed after the originally filed disclosure. It is regretted that the NEW MATTER was not pointed out earlier in these claims.
>
> [1] In claims 325-376 arrays are claimed. These claimed arrays start with the broadest versions in claim 325 as only requiring a substrate surface with double-stranded nucleic acid fixed or immobilized thereto with at least one strand labeled as described in said claim. The closest array description, as filed, is given in the specification on page 16, lines 9-27. In this description the array also is limited to glass plates having depressions or wells with denatured analytes deposited therein, wherein single stranded analytes are fixed to the surfaces of the wells. Chemically labeled probes may then be hybridized to these analytes and subjected to detection of any probe-analyte hybrid. It is noted that the analytes are characterized as being "various" which supports the presence of "different" analytes deposited in each well or depression. It is additionally noted that plastic wells are a disclosed option as given in the bridging sentence between pages 20 and 21 of the instant specification. Polystyrene microfilter wells are described on page 22, lines 10-12, as a solid support. The practice of fixing polynucleotide analytes to conventional microtiter plates is described on page 23 at the start of Example 7. In summary, the array embodiments, as filed, are all at least directed to solid supports with wells or depressions therein. It is lastly noted that instant claim 325 does not require either wells or depressions as being the form of the array of analyte fixation sites nor its being either glass or plastic, wherein microtiter arrays are deemed to be made of plastic.

It is additionally noted that arrays of tubes or cuvettes as given in claim 340 has not been found as filed. Thus, the broader arrays as included in claim 325 contains NEW MATTER. Such broader array embodiments which are NEW MATTER, for example, include flat surface arrays or non-glass or non-plastic arrays. This NEW MATTER is contained in instant claims 325-376.

In the Office Action (page 5, last two lines, through page 9, first full paragraph), the Examiner continued:

[2] The solid support given as "nitrocellulose" is cited in the instant specification on page 10, line 23, but the broader term "cellulose" has not been found as filed. This broader limitation which contains NEW MATTER in the additional breadth over the more limited "nitrocellulose" is present in instant claims 275, 336, 375, 376, 405, 414, 493, 502, 565, 574, 651, and 660.

[3] Several of the instant claims contain the limitation given as "glass-coated". This limitation is NEW MATTER in that glass-coated indicates a solid support which has a coating of glass over it. This coating type has not been found as filed. It is noted that coatings of various types are instantly disclosed such as coating of a solid support with a material which permits linkage, fixation, or immobilization of analytes, for example. Thus, the coating is not glass per se but rather optionally a linker coating on a glass solid support. The phrase "glass-coated" is indicative of a solid support having a glass coating thereon which is NEW MATTER in instant claims 189, 190, 196, 233, 234, 277, 278, 338-341, 375, 376, 407, 408, 414, 451, 452, 495, 496, 502, 567, 568, 574, 610, 611, 653, 654, and 660.

[4] Several of the instant claims contain the limitation given as "plastic-coated". This limitation is NEW MATTER in that plastic-coated indicates a solid support which has a coating of plastic over it. This coating type has not been found as filed. Thus, similar to the above glass-coated NEW MATTER, the plastic-coated NEW MATTER is present in instant claims 191, 192, 196, 235, 236, 279, 280, 409, 410, 414, 453, 454, 497, 498, 502, 569, 570, 574, 612, 613, 655, 656, and 660.

[5] Several of the instant claims contain the limitation given as "oncogene" or combination thereof containing an oncogene. This limitation is NEW MATTER in that the limitation, oncogene, has not been found as filed. The amendment, filed 5/19/99, referred to the reference EP 63879 for support for these limitations. The next paragraph, below, explains why this is improper incorporation by reference and supports this rejection. The following claims contain this NEW MATTER: 205, 206, 245, 246, 293,294, 348, 349, 375, 376, 423, 424, 463, 464, 511, 512, 582, 583, 621, 622, 668, and 669.

[6] Several of the instant claims contain limitation directed to specific types of mutations given as deletion, insertion, inversion, point mutation, and a combination thereof. These limitations are NEW MATTER in that the limitations have not been found as filed. It is noted that the amendment, filed 5/19/99, indicated that these mutation types could be found in the publication EP 63879, cited on

pages 7-8 of the instant specification. Consideration of this page 7-8 citation reveals that it was cited as a reference which reviewed non-radioactive signalling and bridging/signalling systems. It was not cited for any other disclosure. This is an incorporation by reference of pointed to subject matter but not other subject matter. Such incorporations by reference must be directed to particular disclosures for them to be usable for giving written basis for claim limitations.. A specific claim limitation is clearly essential subject matter. It is improper to incorporation by reference essential subject matter cited in a foreign patent application. It is improper to generically cite such a reference and then utilize it for anything therein without defining in the citation what it is cited for. In this case the publication was cited for non-radioactive signalling etc. review and not for mutation types. Thus, it does not serve as a proper basis for incorporating mutation types into the instant claims. For further discussion, see the M.P.E.P. at section 608.01(p), part I, subsection A. The following claims contain this NEW MATTER: 206, 246, 294, 349, 375, 376, 424, 464, 512, 583, 622, and 669.

[7] Several of the instant claims contain the limitation given as "partially double-stranded". This limitation is NEW MATTER in that the limitation has not been found as filed. In the amendment, filed 5/19/99, Examples 1-7 were cited for support. Consideration of said Examples 1-7 has failed to reveal written basis for this limitation. The following claims contain this NEW MATTER: 207, 247, 295, 345, 375, 376, 425, 465, 513, 584, 623, and 670.

[8] Several of the instant claims contain the limitation given as "aminopropyltriethoxysilane". This limitation is NEW MATTER in that the closest limitation as filed is given as the more limited material: gamma-aminopropyltriethoxysilane. This material is cited in the instant specification on page 15, lines 26-27. The added breadth of this material without also being of the "gamma" type is NEW MATTER. The following claims contain this NEW MATTER: 328, 375, 376, 379, 387, 395, 539, 547, 555, 696, 704, and 712.

[9] Several of the instant claims contain the limitation given as "a dispersive compound". This limitation is NEW MATTER because this broad concept of a dispersive compound has not been found as filed. The following claims contain this NEW MATTER: 330, 331, 375, 376, 381, 382, 389, 390, 397, 398, 541, 542, 549, 550, 557, 558, 698, 699, 706, 707, 714, and 715.

The new matter rejection is respectfully traversed.

In order to address each and every point raised in the new matter rejection above, Applicants' attorney has inserted bold bracketed numbers. The remarks below are directed to those points designated by the bold bracketed numbers.

[1] With respect to the array issue, it is important to note that new claims 718-872 are all directed to a solid support comprising an array of substrate surfaces. The fixation or immobilization of nucleic acid to a solid support, including

the aforementioned array of substrate surfaces, is an inventive concept universally disclosed throughout Applicants' original specification. Applicants' invention has spawned innumerable useful applications in nucleic acid technology, including detection, genetic and sequence analysis, and drug screening. Applicants' inventive concept can be best understood by viewing two charts which have been prepared from the specification at hand. Attached as Exhibit 2, the first chart shows the interrelationship between the solid support and various other elements or embodiments, including nature of the support material, surface treatments, devices, apparatus and, of course, the array subject matter. List on the second chart which is attached as Exhibit 3, are citations to the specification which support the various elements, embodiments and relationships.

At the outset, it must be kept in mind that the above-quoted statement in the new matter rejection (page 16, lines 9-27) is only a *part* of Example 1 (specification, pages 15-16), and this is an example which uses a "glass support" and a borosilicate "glass surface," neither of which embodiment has "wells or depressions."

The statement immediately preceding Example 1 on page 15 in the specification states:

> DETAILED DESCRIPTION
>
> The following examples are illustrative of preferred embodiments of the method of the present invention. Specifically referred to therein are methods for fixing the analyte to a **non-porous solid support**, as well as illustrations of the use of soluble signals in polynucleotide probes as discussed above.

The rest of the examples (2-7) disclose a number of different forms of the non-porous solid support stated above, including:

Example 2: **glass surface** of Example 1
Example 3: activated **glass surface** (**glass tubes**)
Example 5: **plastic surface**
plastic plates
Example 6: **polystyrene plates**
non-porous siliceous solid support,
such as **glass** and **plastic**
Example 7: conventional **microtiter well plates**

The passage cited in the new matter rejection (page 16, lines 9-27) begins with the introductory phrase "***For example***, . . ." Thus, the use of glass plates (or plastic plates which the Examiner is willing to allow) with wells or depressions is but an example of the claimed array.

Significantly, other portions in the specification disclose the array subject matter *without limitation* to "wells or depressions." To begin with, the specification quite clearly and significantly *equates* "device" with "solid support" in the first paragraph on page 14:

> . . . ***It may also be desirable for*** both the solid support to which the analyte is fixed and the device to be composed of the same material, or for ***the device to function as the support*** in addition to facilitating spectrophotometric detection.

"Devices" are also described later in the second paragraph on page 14:

> . . . A related product of the invention is an apparatus comprising a **plurality of such devices** for containing a fluid, **in which at least one such device contains the above-described immobilized polynucleotide sequence**, polynucleotide or oligonucleotide probe, signalling moiety, and soluble signal.

The devices referenced above in page 14, first paragraph, are further described variously in the specification. For example, beginning with the last four lines on page 13, and continuing through the first line on page 14 in the specification, it is disclosed:

> . . . ***Examples of devices*** useful in the spectrophotometric analysis of the signal include ***conventional apparatus*** employed in diagnostic laboratories, i.e., plastic or glass wells, tubes, cuvettes or arrangements of wells, tubes or cuvettes.

Continuing on page 14, lines 19-20, it is also disclosed:

> . . . The ***portion of the device for containing the fluid*** is desirably a ***well, a tube, or a cuvette***.

Other description for the "device" is found in originally filed claim 17 from the original specification:

> Claim 17. The method in accordance with Claim 16, characterized in that said ***device*** is selected from the group consisting of ***a well, a tube, a cuvette and an apparatus which comprises a plurality of said wells, tubes or cuvettes***.

"Means for containing a fluid" is also defined by originally filed claim 23 in the specification:

Claim 23 An **apparatus** comprising:

a **plurality of means for containing a fluid**, wherein at least one of said means comprises:

(i) an ***immobilized polynucleotide sequence hybridized to a polynucleotide or oligonucleotide probe***, said probe having covalently attached thereto a chemical label comprising a signalling moiety capable of forming a soluble signal, and

(ii) a soluble signal generated by means of said signalling moiety.

Furthermore, the above-recited means for containing a fluid is also found in originally filed claim 21 from the specification:

Claim 21. The ***device*** according to Claim 20, wherein said ***means for containing a fluid*** is selected from the group consisting of ***a well, a tube, and a cuvette***.

It should not be overlooked that the portion in the disclosure cited in the new matter rejection refers to "the single-stranded analytes being fixed to the ***surfaces*** of the wells." Just as in the case of any non-porous solid support, or any device, or any means for containing a fluid, or any well or depression, or any tube or cuvette, it is ultimately the ***surface of such support*** (or device, means for containing a fluid, well or depression, tube or cuvette) to which the oligo- or polynucleotides are fixed or immobilized. The fact that the oligo- or polynucleotides are fixed or immobilized to the surfaces of such elements is seen in several instances in the specification:

a) Example 2

"A ***glass surface*** as described in Example 1 can be employed . . .

b) Example 3

. . . In these tests, the analyte, phage lambda DNA, was immobilized on an activated ***glass surface*** . . .

c) Example 5

The advantages of the practices of this invention are also obtainable when the probe is immobilized on a ***non-porous plastic surface***. When a ***plastic surface*** is employed, it is sometimes desirable to increase the effectiveness or uniformity of the fixation by pretreating the ***plastic surface***.

Because polystyrene from various batches or sources exhibits different binding capacities, the adherence or fixing of DNA to a ***polystyrene surface*** is improved by ***treating the surface*** with an amino-substituted hydrophobic polymer or material. . . Another

technique for improving the fixing or uniformity of the ***plastic surface*** for fixing DNA involves ***treatment of the surface*** with polylysine (PL).

In tests involving the fixing the DNA to a ***plastic surface***, biotinylated DNA (bDNA) was denatured and aliquoted into Dynatech, Immulon II™ removeable wells.

d) Example 6

An improved capability for fixing or immobilization of DNA to non-porous siliceous solid supports, such as glass and plastic, is also provided by treatment with a coating of an epoxy resin. For example, ***treatment of glass or polystyrene surfaces*** with commercially available epoxy glues, such as a solution of epoxy glue in ethanol [1 percent w/v] serves this purpose. These epoxy solutions are applied to the ***surfaces or wells***, and the solvent, ethanol, evaporated thereon at a temperature of 37° C, thereby providing a polyamine polymeric coating on the ***treated surface***. These ***surfaces*** were found to absorb ^{3}H-labeled DNA from aqueous solution at pH less than 9.5.

It is quite clear and even beyond dispute that Applicants' disclosure covering their claimed solid supports comprising an array of substrate surfaces" extends far beyond the one quoted passage (page 16, lines 9-27).

On the issue of the omitted essential element, the case law fully supports Applicants' claimed array subject matter. As described above, the present specification describes the claimed array without limitation to "wells or depressions." Generally, the test for the "omitted essential element" is whether or not a person skilled in the art would have understood the element(s) to be essential to the disclosed invention. In this case, properly phrased, the test for the "omitted essential element" is whether a person skilled in the art would have understood "wells or depressions" to be essential elements of our claimed array. The omitted essential element rule cannot be applied to the present case and claims which can be wholly distinguished from *Gentry*, the leading case and controlling authority on the doctrine.

1. In the *Gentry* case [Gentry Gallery, Inc. v. Berkline Corporation, 134 F.3d 1473 (Fed. Cir. 1998), 45 USPQ2d 1498 (Fed. Cir. 1998)], the issue was whether the placement of controls on a console in a reclining sofa was an *essential* element of the invention in the original application. A copy of the *Gentry* case is

attached as Exhibit 4. After reviewing the Objects of the Invention, the scope of the claims submitted with the original application and other descriptions in the specification, the Court ruled that the location of the recliner control on the console was an "essential element" of the described invention. [134 F.3d at 1479, 45 USPQ2d at 1503]. The Court reached this conclusion because no other disclosure could be found in the original application for placing the controls on a console in a *different* position on the sofa. In other words, "the inventor did not have an alternate location in mind when he made his initial disclosure," to borrow from the *Reiffin* case, discussed *infra*. Here, as described above, wells or depressions are not defined to be essential elements of the claimed array because

- the example itself (Example 1, pages 15-16) is drawn to a "***glass surface***" and a "***borosilicate glass surface***"
- All of the examples (1-7) are stated to be illustrative of preferred embodiments . . . and method for ***fixing*** . . . ***to a non-porous solid support***.
- The passage cited in the new matter rejection (page 16, lines 9-27) begins with the introductory phrase "***For example***, . . .
- Arrays are disclosed in other portions of the specification without limitation to "wells or depressions," including a ***plurality of devices for containing a fluid***" and "a ***plurality of means for containing a fluid***."
- Devices, including the array device (an ***apparatus comprising a plurality of devices for containing a fluid***, page 14, lines 21-26) are likewise not limited to "wells or depressions."
- Moreover, ***any device in this invention can function as a*** [non-porous] ***solid support***, as well as be composed of the same material.

2. In the *Reiffin* case [Reiffin v. Microsoft Corp., 48 USPQ2d 1274 (N.D. Calif. 1998), another case involving an issue of the omitted essential element, summary judgment for the defendant was granted and the plaintiff's patent was invalidated based on the omission of four elements deemed to be essential to describe the plaintiff's patented invention for a "multithreading" computer technology. In that case which cited the *Gentry* case prominently, the California District Court examined the "Summary of the Invention," the abstract, the "Object of the Invention," the "Description of Prior Art," and the originally filed claims,

before ruling that essential elements had been omitted from the issued claims. The Court also noted that at least one of the four elements was referenced in each of the patent's 21 original claims. A copy of the *Reiffin* case is attached as Exhibit 5.

In summary, the specification does not limit the claimed array to "wells or depressions," even in the disclosure (page 16, lines 9-27) cited in the rejection which is only given as an "example." Other disclosure is provided in the specification where solid supports comprising an array of substrate surfaces are described as devices or means for containing a fluid, and such devices or means are not limited to wells or depressions, but can include tubes or cuvettes, or arrangements of wells, tubes or cuvettes. More importantly, devices are specifically stated to "function as the [solid] support" (page 14, lines 1-5), and as set forth in the support charts (Exhibits 2 and 3), the surfaces used in the solid supports can take many forms and can be made from many different kinds of materials. Further, these materials can be treated in many ways to facilitate fixation or immobilization of nucleic acid thereon. Moreover, it is the surface of the solid support (or device or array or apparatus or means for containing a fluid or even the "wells or depressions") to which the oligo- or polynucleotides are ultimately being fixed or immobilized. The presence or absence of "wells or depressions" is immaterial to the present invention and claims whereby oligo- or polynucleotides have been fixed or immobilized to the surfaces of non-porous solid supports.

[2] The broader term "cellulose" has been expunged from the new claims which recite "nitrocellulose" in various dependent claims.

[3] [4] It is believed that the use of the terms "glass-coated" and "plastic-coated" is adequately described in the specification. It is equally reasonable to interpret the claims containing these terms to mean that the surface has been treated with an agent. As described in **[1]** above with respect to the array issue, several portions and examples in the specification relate to coating glass or plastic surfaces. See Examples 1-2 and 4-6. In the first paragraph of Example 3, it is stated that "glass tubes were coated with 100 µl of coating solution [50 percent formamide, 5X SSC, 100 µg salmon sperm DNA, 0.2 percent polyvinylpyrrolidone, 0.1 percent Triton X-100, 0.2 percent BSA and 0.05 percent SDS] at 42° C for 90-120 minutes." In Example 6, page 22, last paragraph, it is disclosed that "[a]n

improved capability for fixing or immobilization of DNA to non-porous siliceous solid supports, such as glass and plastic, is also provided by treatment with a coating of an epoxy resin." The other examples also support the use of "glass-coated" and "plastic-coated" in the claims. Thus, the use of these terms in the claims is adequately described in the specification.

[5] Under the legal test for written description, adequate disclosure must be supported in the specification through express, implicit or inherent disclosure. To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *In re Robertson*, 49 USPQ2d 1949 (Fed. Cir. 1999). In the Summary of the Invention (page 9, lines 16-24), the nucleic acid sequence to be detected is referred to as "an analyte:"

> The present invention provides a solution for the disadvantages of presently available methods of detecting analytes by a novel combination of hybridization and immunological techniques. In accordance with the practice of the present invention, chemically labelled polynucleotide or oligonucleotide probes are employed to detect analytes by having the capacity to generate a reliable, easily quantifiable soluble signal.

In the specification, beginning on page 1, last three lines, and continuing through the first eight lines on page 2, Applicants define analytes:

> Analytes - A substance or substances, either alone or in admixtures, whose presence is to be detected, and if desired, quantitated. The analyte may be DNA or RNA molecule of small or high molecular weight, or molecular complex including those molecules, or a biological system containing nucleic acids, such as a virus, a cell, or group of cells. Among the common analytes are nucleic acids (DNA and RNA) or segments thereof, oligonucleotides, either single- or double-stranded, viruses, bacteria, cells in culture, and the like . . .

Oncogenes are, of course, nucleic acid for which the description in the specification constitutes a generic disclosure of "oncogenes." It is reasonable to expect that a person of ordinary skill in the art at the time Applicants' invention was made would have recognized that oncogenes would be included among nucleic acid sequences to be analyzed. As stated in the rejection, EP 63879 was cited as a reference which reviewed non-radioactive signalling and bridging/signalling systems. To a person of ordinary skill in the art, such as review would necessarily

entail particular nucleic acid formats, separation and enrichment steps, as well as the nature of the analyte whose presence or characteristics are sought - and oncogenes would naturally and inherently be included among such analytes.

To further elaborate, EP 63879 discloses that nucleic acids may be detected in a number of places. The abstract contains a general disclosure, stating:

> Applications include detection and localization of polynucleotide sequences in chromosomes, fixed cells, tissue sections, and cell extracts. Specific applications include chromosomal karyotyping, clinical diagnosis of nucleic acid-containing etiological agents, e.g., bacteria, viruses, or fungi, and diagnosis of genetic disorders.

Reference should also be made to page 9 in EP 63879 where it is stated:

> Some uses include detecting and identifying nucleic acid-containing etiological agents, e.g. bacteria and viruses; screening bacteria for antibiotic resistance; diagnosing genetic disorders, e.g., thalassemia and sickle cell anemia; chromosomal karyotyping; and identifying tumor cells.

A further description in EP 63879 is found on page 43, lines 13-21 where it discloses:

> Finally tumor cells can be diagnosed by preparing polynucleotides which are modified according to this invention and are complementary to the messenger ribonucleic acid synthesized from a deoxyribonucleic acid gene sequence associated with the production of polypeptides, such as alpha-fetal protein or carcinoembryonic antigen, the presence of which is diagnostic for specific tumor cells. Hybridization and detection of hybrid duplexes thus would provide a method for detecting the tumor cells.

Claim 54 in EP 63879 specifically recites the above-described method.

In conclusion, a person of ordinary skill in the art would expect that a review of non-radioactive signalling and bridging/signalling systems, such as disclosed in EP 63879, would also embrace information on the types of nucleic acids to which such systems could be usefully employed.

[6] Just as in the case of "oncogenes," EP 63879 discloses in its review of non-radioactive signalling and bridging/signalling systems, applications such as

the diagnosis of genetic disorders, particularly thalassemia and sickle cell anemia. See page 9 in EP 63879, quoted above. Both of these genetic disorders result from specific types of mutations. Additional disclosure is provided in EP 63879 on page 35, lines 4-11 and in claims 49-50. In the former, it is disclosed:

> This approach can be extended to the diagnosis of genetic disorders, such as thalassemia and sickle cell anemia. The deoxyribonucleotide(sic) acid gene sequence whose presence or absence (in the case of thalassemia) is associated with the disorder can be detected following hybridization with a polynucleotide probe according to this invention based upon complex formation with a suitable detectable polypeptide.

See also claim 49 (page 67) and 50 (pages 67-68) in EP 63879.

Thus, the recitation of mutations is adequately disclosed in the specification.

[7] It is believed that the use of "partially double-stranded" in the new claims is adequately described in Applicants' disclosure. If not expressly described by any of the examples, "partial double-strandedness" would at least be implicitly or inherently disclosed by the use of the generic term "double-stranded." As any ordinarily skilled artisan would recognize, the length of probe sequences and analyte sequences are often if not most of the time of different lengths. Thus, whenever a labeled nucleic acid or sequence hybridizes with its complementary strand or sequence, a partially double-stranded "composition" often results.

[8] With regard to the issue of "aminopropyltriethoxysilane," this element is no longer present in the new claims. Instead, the term "γ-aminopropyltriethoxysilane" is used to designate this particular types of surface treatment agent. Applicants note that the Weetall and Filbert publication cited on page 16, lines 3-7) discloses "γ-aminopropyltriethoxysilane."

In light of the new claims and foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the new matter rejection.

The Rejection Under 35 U.S.C. 112, First Paragraph

Claims 183-318 and 377-717 stand rejected for indefiniteness under 35 U.S.C. §112, second paragraph. In the Office Action (pages 9-11), the Examiner stated:

> **[1]** Comparison of instant claims 183 and 185 causes both claims to be vague and indefinite as to what is meant for the claimed subject matter. In claim 183, line 2, the system is described as being non-porous but confusingly the claim lacks any actual items in the system which are then pointed to as being non-porous. Also, there is no indication whether the non-porous limitations in claim 183 are meant for all system items or only a portion of the system. Claims 185-187 then further confuse the system characterization in that the solid support has therein a porous option. In reviewing the instant specification, the solid support in claim 183 seems to be the only overtly cited item in the claimed system that would be reasonably described as corresponding to the non-porous item in line 2 of claim 183, but, in conflict, it limited as an option to being porous in claim 185. Clarification as to what metes and bounds such as actual system items are non-porous in claim 183 is requested via clearer claim wording, including clarifying what is non-porous in the practice of the system of claims 185-187 when the solid support is porous. This same concern exists for claims 231, 271, 401, 449, 489, 561, 608, 647, and those dependent therefrom as confusingly mixing porous and non-porous limitations.
>
> **[2]** Claim 184 is vague and indefinite as to what is meant by the solid support both being within the system as well as being a part of the system due to its dependence from claim 183. Other similar dependent claims are rejected hereinunder due to this issue, such as claim 272 etc. Clarification via clearer claim wording is requested.
>
> **[3]** Claim 188 is vague and indefinite in defining a selection of options but does not clarify whether the solid support is therein limited to being the non-porous option from claim 185.
>
> **[4]** Claims 204 and 205 cite the phrase "to be identified" which lacks antecedent basis in claim 183 from which they depend because only quantitation is cited in said claim 183. Claims dependent from claim 204 also contain this antecedent basis issue. Claims 244, 245, 292, 293, 422, 423, 462, 463, 510, 511, 581, 582, 620, 621, 667, 668, etc. also contain this issue. Similarly, claims 229, 269, 317, 447, 487, 535, 606, 645, 692, and claims dependent therefrom cite "detectable" which lacks antecedent basis due to only quantitation being cited in claims from which they depend.

The indefiniteness rejection is respectfully traversed.

The remarks below are directed to the four points in the above rejection which have been designated by bold bracketed numbers.

[1] It is believed that this issue has been obviated by the presentation of the new claims, the drafting of which took this matter into account.

[2] Again, the new claims are believed to be more definite and clear with respect to the relationship between the solid support and the system.

[3] The nature of the "solid support" is believed to be clarified by the presentation of the new claims.

[4] The inadvertent reference to "identified" in the composition and system claims 873-1110) is believed to have been obviated by the presentation of the new claims and language which are directed to the "quantification" aspects of Applicants' invention.

In view of the new claims, it is believed that all issues relating to indefiniteness have been obviated. Reconsideration and withdrawal of the rejection under the second paragraph of §112 is respectfully requested.

The First Rejection Under 35 U.S.C. 102(b)

Claims 561-563, 571, 574, 575, 577, 578, 580-582, 585-609, 612-614, 617, 619-621, 624-649, 652, 655-657, 660, 661, 663, 664, 666-668, and 671-693 stand rejected under 35 U.S.C. §102(b) as being anticipated by Kourilsky et al. (UK 2,019,408). In the Office Action (pages 11-12), the Examiner stated:

> As previously described of record Kourilsky et al. discloses the centrifugal fixation of a target/probe hybrid with a chemical label thereon on page 3, lines 18-54, with evaluation of bound probe via a P-galactosidase in solution of the resuspended hybrids. Instant claim 561 requires at least three items: a solid support, fixed double-stranded oligonucleotide or polynucleotide, and a chemical label which may be quantified in solution via dye, chromogen, enzyme, etc. given the complex character of the label of Kourilsky et al. These items are cited above as being disclosed by Kourilsky et al. The quantitation limitations in instant claim 561, for example, is a capability which clearly is present considering the solution enzyme determination of Kourilsky et al. and thus is anticipated by the reference, even though Kourilsky et al. does not perform the quantitation while the hybrids are

> still fixed on the support. Also, centrifuge tubes for such a centrifugal procedure are well known to be made of translucent, non-porous, plastic. Several added instant limitations directed to various bridging moieties and immobilization via hybridization of the probe are deemed anticipated by the the somewhat complex assemblage of the probe/target hybrid and label moieties in that portions are direct, portions are indirect, etc. The probe is clearly immobilized via hybridization. Otherwise the assay would be non-functional if non-hybridized probe also was fixed by the centrifugation step.
>
> The first anticipation rejection is respectfully traversed.

As noted in the opening remarks of this paper, all of the composition and system claims recite the element of "photometric means for quantifying said quantifiable signaling entity or entities." Thus, a complete lack of identity exists between Kourilsky's disclosure and Applicants' claimed invention.

In view of the new composition and system claims submitted above, Applicants respectfully request that the first anticipation rejection be withdrawn upon further reconsideration.

The Second Rejection Under 35 U.S.C. 102(b)

Claims 183-185, 188, 189, 197-201, 203-205, 208-223, 225-227, 229-233, 240, 241, 243-245, 248-263, 265-267, 269-273, 276, 277, 285-289, 291-293, 296-311, 313-315, 317, 318, 377, 385, 393, 401-403, 406, 407, 415-419, 421-423, 426-441, 443-445, 447-451, 458, 459, 461-463, 466-481, 483-485, 487-491, 494, 495, 503-507, 509-511, 514-529, 531-533, 535-537, 545, 553, 561-563, 566, 567, 575-578, 580-582, 585-600, 602-604, 606-610, 617, 619-621, 624-639, 641-643, 645-649, 652, 653, 661-664, 666-668, 671-686, 688-690, 692-694, 702, and 710 stand rejected under 35 U.S.C. §102(e) as being clearly anticipated by Stuart et al., U.S. Patent No. 4,732,847 or Ward et al., U.S. Patent No. 4,711,955. In the Office Action (pages 13-14), the Examiner stated:

> Stuart et al. discloses the practice of in-situ hybridization on a coverslip with fluorescent antibody detection of probe/target hybrids in column 6, lines 17-57, which anticipates the above instant claims. The target samples were prepared on acid washed microscope slides as indicated in column 4, lines 61-67. The slides and coverslips at the time were well known to be transparent glass and non-porous and

form a system. The acid washing is deemed a surface treatment as required in instant claim 377, for example. The fluorescent labeling is deemed a type of chemical label because instant dependent claims such as claim 221 includes fluorescent labeling in the signalling limitations. It is noted that Stuart et al. does not disclose quantitation of signal but it is also noted that the instant claims are directed to a capability for quantitation of label and are not method claims. A fluorescent label as utilized in Stuart et al. emits light which is well known to be quantifiable and thus anticipates the instant claims listed above. See the below paragraph which cites legal decisions as to shifting the burden to applicants to distinguish the reference disclosure over the invention when the claimed subject matter is expected to anticipate the claimed invention by having properties cited in the instant claims but not measured in a cited prior art reference. Ward et al. also cites in-situ hybridization with detection with avidin-peroxidase in columns 19-20 therein which reads on the above claims also due to the emininent quantifiability of such signals.

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

As noted in the opening remarks of this paper and in the preceding first anticipation rejection, all of the composition and system claims recite the element of "photometric means for quantifying said quantifiable signaling entity or entities." Thus, a complete lack of identity exists between either of the cited Stuart and Ward disclosures and Applicants' claimed invention.

In view of the new composition and system claims submitted above and the recitation of "photometric means," Applicants respectfully request reconsideration and withdrawal of the second anticipation rejection.

Submission of Art-Related Documents

Applicants' attorney is presently searching for any or all art-related documents related to the claimed subject matter. As soon as that search has been completed, Applicants will submit such art-related documents in an Information Disclosure Statement for consideration by the Examiner.

* * * * * * *

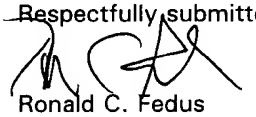
SUMMARY AND CONCLUSIONS

Former claims 183-318 and 325-717 have been canceled in favor of new claims 718-1110 which are presented for further examination on the merits.

The fee for adding new claims 718-1110 is $3,222, is based upon the large entity fee for 179 additional claims above the 649 claims previously paid [179 claims X $18 = $3,222]. No additional independent claims are represented by the new claims. As indicated in the accompanying Transmittal form, authorization is hereby given to charge the amount of $3,222 to Deposit Account No. 05-1135. This Amendment is also accompanied by a Request For An Extension Of Time (3 months) and authorization for the large entity fee therefor. No other fee or fees are believed due in connection with this filing. In the event that any other fee or fees are due, however, The Patent and Trademark Office is hereby authorized to charge the amount of any such fee or fees to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,



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